PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of tau protein kinase 1, such as Alzheimer disease and the like.

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and amyloid β protein has been elucidated as their main component (abbreviated as "Aβ" hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4,

2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of Aβ (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, Aβ abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of Aβ (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of Aβ is involved in cellular death due to ischemic cerebrovascular disorders.

Other diseases in which abnormal accumulation and agglomeration of Aβ are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined

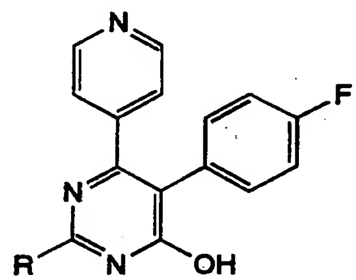
Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3β, FEBS Lett., 325, 167 (1993)).

It has been reported that Aβ, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why Aβ causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by Aβ treatment of fetal rat hippocampus primary culture system, and then found that the TPK1 activity was increased by Aβ treatment and the cell death by Aβ was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of Aβ. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

As structurally similar compounds to the compounds of the present

invention represented by formula (I) described later, compounds represented by the following formula (A) are known:



(A)

wherein R represents 2,6-dichlorobenzyl group, 2-(2-chlorophenyl)ethylamino group, 3-phenylpropylamino group, or 1-methyl-3-phenylpropylamino group (WO98/24782). The compounds represented by formula (A) are characterized to have 4-fluorophenyl group at the 5-position of the pyrimidine ring, and not falling within the scope of the present invention. Moreover, main pharmacological activity of the compounds represented by formula (A) is anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) are useful as a TPK1 inhibitor or a medicament for therapeutic treatment of neutodegenerative diseases, and therefore, their pharmacological activities are totally different to each other.

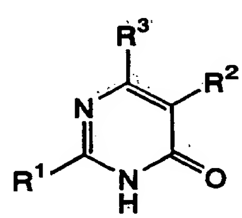
Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease and the like. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment

of the diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of Aβ and the formation of the PHF and by inhibiting the drop of nerve cells.

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



(I)

wherein R^1 represents a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a C_1-C_{18} alkyloxy group which may be substituted, a C_3-C_{18} alkenyloxy group which may be substituted, a C_3-C_{18} alkynyloxy group which may be substituted, a C_3-C_8 cycloalkyloxy group which may be substituted, a C_6-C_{14} aryloxy group which may be substituted, a heterocyclic group which may be substituted, or a group

represented by $-N(R^4)\text{-}W\text{-}R^5$ wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond, carbonyl group, sulfonyl group, or a nitrogen atom which may be substituted with a C_1-C_{18} alkyl group which may be substituted;

R^2 represents hydrogen atom, hydroxyl group, a C_1-C_8 alkyl group which may be substituted, a C_3-C_8 alkenyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_1-C_8 alkyloxy group which may be substituted, a C_3-C_8 cycloalkyloxy group which may be substituted, a C_6-C_{14} aryloxy group which may be substituted, a C_1-C_8 alkylthio group which may be substituted, a halogen atom, nitro group, cyano group, an amino group which may be substituted, carboxyl group, a C_1-C_8 alkyloxycarbonyl group which may be substituted, a C_3-C_8 cycloalkyloxycarbonyl group which may be substituted, carbamoyl group, a C_1-C_8 alkylaminocarbonyl group which may be substituted, or a C_1-C_8 dialkylaminocarbonyl group which may be substituted; and

R^3 represents a pyridyl group which may be substituted.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, and the aforementioned medicament which is

used for preventive and/or therapeutic treatment of neurodegenerative diseases. As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia; and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives. The present invention further provides an inhibitor of tau protein kinase 1 comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

Best Mode for Carrying Out the Invention

The "alkyl group" or an alkyl portion of a functional group containing the alkyl portion (alkoxyl group, for example) used herein may be either linear or branched. The C_1-C_{18} alkyl group represented by R^1 may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group or octadecyl group. In the specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited. and when two or more substituents are present, they may be the same or different.

When the C_1-C_{18} alkyl group represented by R^1 has one or more substituents A, the alkyl group may have one or more substituents A selected form the group consisting of a C_3-C_8 cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, and cyclooctyl group; a C_6-C_{10} aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group; a C_3-C_8 cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group; fluorenyl group; a C_1-C_5 alkoxyl group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C_6-C_{14} aryloxy group such as phenoxy group, and naphthoxy group; a C_1-C_5 alkylthio group such as

methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C_6-C_{14} arylthio group such as phenylthio group, and naphthylthio group; a C_1-C_5 alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a C_6-C_{14} arylsulfonyl group such as phenylsulfonyl group, and naphthylsulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C_1-C_5 halogenated alkyl group such as trifluoromethyl group; hydroxyl group; nitro group; oxo group; formyl group; a C_2-C_6 alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C_1-C_5 monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C_2-C_{10} dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; and a residue of heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring,

phthalazine ring, naphtylidine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like.

When an aryl group or a heterocyclic group is present as a substituent, the group may have one or more substituents B selected form the group consisting of a C_1-C_{18} alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, hexyl group, isohexyl group, heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, and octadecyl group, and the aforementioned substituent A.

Examples of the C_3-C_{18} alkenyl group represented by R^1 include, for example, allyl group, 2-butenyl group, 3-butenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 2-methyl-2-butenyl group, 3-methyl-2-butenyl group, 2-hexenyl group, 5-hexenyl group, 2-heptenyl group, 6-heptenyl group, 2-octenyl group, 7-octenyl group, 2-nonenyl group, 8-nonenyl group and the like, and examples of the C_3-C_{18} alkynyl group represented by R^1 include, for example, propargyl group, 2-butynyl group, 3-butynyl group, 2-pentynyl group, 3-pentynyl group, 4-pentynyl group, 1-methyl-2-pentynyl group, 4-methyl-2-pentynyl group, 2-hexynyl group, 5-hexynyl group, 2-heptynyl group, 6-heptynyl group, 2-octynyl group, 7-octynyl group and the like. These groups may be substituted with one or more substituents A.

Examples of the C_3-C_8 cycloalkyl group represented by R^1 include, for example

example, cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like, and examples of the C_6-C_{14} aryl group represented by R^1 include, for example, phenyl group, naphthyl group, anthryl group and the like. These groups may be substituted with one or more substituents B. The C_6-C_{14} aryl group represented by R^1 may further have one or more substituents selected from the group consisting of a hydroxyalkyl group such as hydroxymethyl group, 1-hydroxyethyl group, 2-hydroxyethyl group, and 3-hydroxypropyl group; a C_1-C_3 alkyl group having a C_1-C_6 alkylcarbonyloxy group such as formyloxymethyl group, acetoxymethyl group, 1-acetoxyethyl group, 2-acetoxyethyl group, 3-acetoxypropyl group, propionyloxymethyl group, butyryloxymethyl group, and valeryloxymethyl group; a C_1-C_3 aminoalkyl group such as aminomethyl group, 1-aminoethyl group, 2-aminoethyl group, and 3-aminopropyl group; a monoalkylamino(C_1-C_3 alkyl) group having a C_1-C_8 alkyl group on the nitrogen atom such as methylaminomethyl group, ethylaminomethyl group, 1-methylaminoethyl group, 2-methylaminoethyl group, and 3-methylaminopropyl group; and a dialkylamino(C_1-C_3 alkyl) group having the same or different C_1-C_8 alkyl groups on the nitrogen atom such as dimethylaminomethyl group, diethylaminomethyl group, 1-dimethylaminoethyl group, 2-dimethylaminoethyl group, and 3-dimethylaminopropyl group.

Examples of the C_1-C_{18} alkyloxy group represented by R^1 include, for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group, hexyloxy group, isohexyloxy group, heptyloxy group, octyloxy group, nonyloxy group, decyloxy group, undecyloxy group,

dodecyloxy group, tridecyloxy group, tetradecyloxy group, pentadecyloxy group, octadecyloxy group and the like. Examples of the C_3-C_{18} alkenyloxy group represented by R^1 include, for example, allyloxy group, 2-butenyloxy group, 3-butenyloxy group, 2-pentenyloxy group. 3-pentenyloxy group, 4-pentenyloxy group, 2-methyl-2-butenyloxy group. 3-methyl-2-butenyloxy group, 2-hexenyloxy group, 5-hexenyloxy group. 2-heptenyloxy group, 6-heptenyloxy group, 2-octenyloxy group, 7-octenyloxy group, 2-nonenyloxy group, 8-nonenyloxy group and the like. Examples of the C_3-C_{18} alkynyloxy group represented by R^1 include, for example, propargyloxy group, 2-butynyloxy group, 3-butynyloxy group, 2-pentynyloxy group, 3-pentynyloxy group, 4-pentynyloxy group, 1-methyl-2-pentynyloxy group, 4-methyl-2-pentynyloxy group, 2-hexynyloxy group, 5-hexynyloxy group, 2-heptynyloxy group, 6-heptynyloxy group, 2-octynyloxy group, 7-octynyloxy group and the like. These groups may be substituted with one or more substituents A.

Examples of the C_3-C_8 cycloalkyloxy group represented by R^1 include, for example, cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group, and examples of the C_6-C_{14} aryloxy group represented by R^1 include, for example, phenoxy group, naphthoxy group, and anthryloxy group. These groups may be substituted with one or more substituents B.

Examples of the heterocyclic group represented by R^1 include, for example, residues of heterocyclic rings having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, isobenzofuran ring, chromene ring, chroman ring,

isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring. pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphtylidine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like. The heterocyclic group may have one or more substituents B.

As the optionally substituted C_1-C_{18} alkyl group, and as the optionally substituted C_3-C_{18} alkenyl group, the optionally substituted C_3-C_{18} alkynyl group, the optionally substituted C_3-C_8 cycloalkyl group, and the optionally substituted C_6-C_{14} aryl group which are independently represented by R^4 and R^5. such as those explained as to R^1 may be used. When the symbol "W" represents nitrogen atom, as the optionally substituted C_1-C_{18} alkyl that may be present on the nitrogen atom, such as those explained as to R^1 may be used.

Examples of the C_1-C_8 alkyl group represented by R^2 include, for example, methyl group, ethyl group, n-propyl group. isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group. n-hexyl group, isohexyl group. n-heptyl group, n-octyl group and the like, and examples of the C_3-C_8 alkenyl group represented by R^2 include. for example, allyl group,

2-butenyl group, 3-butenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 2-methyl-2-butenyl group, 3-methyl-2-butenyl group, 2-hexenyl group, 5-hexenyl group, 2-heptenyl group, 6-heptenyl group, 2-octenyl group, 7-octenyl group and the like. These groups may be have one or more substituents A.

Examples of the C_1-C_8 alkyloxy group represented by R^2 include, for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group, hexyloxy group, isohexyloxy group, heptyloxy group, octyloxy group and the like. Examples of the C_1-C_8 alkylthio group represented by R^2 include, for example, methylthio group, ethylthio group, propylthio group, isopropylthio group, butylthio group, isobutylthio group, sec-butylthio group, tert-butylthio group, pentylthio group, isopentylthio group, neopentyl thio group, 1,1-dimethylpropylthio group, hexylthio group, isohexylthio group, heptylthio group, octylthio group and the like. These groups may be have one or more substituents A.

Examples of the C_1-C_8 alkyloxycarbonyl group represented by R^2 include, for example, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group, isopentyloxycarbonyl group, neopentyloxycarbonyl group, 1,1-dimethylpropyloxycarbonyl group, hexyloxycarbonyl group, isohexyloxycarbonyl group, heptyloxycarbonyl group, octyloxycarbonyl group and the like, and examples of the C_3-C_8 cycloalkyloxycarbonyl group represented by R^2 include, for example, cyclopropyloxycarbonyl group, cyclobutyloxycarbonyl group,

cyclopentyloxycarbonyl group, cyclohexyloxycarbonyl group, cycloheptyloxycarbonyl group, cyclooctyloxy carbonyl group and the like. The aforementioned cycloalkyloxycarbonyl groups may have one or more substituents B, and the aforementioned alkyloxycarbonyl groups may have one or more substituents A.

Examples of the C_1-C_8 alkylaminocarbonyl group represented by R^2 include, for example, methylaminocarbonyl group, ethylaminocarbonyl group, propylaminocarbonyl group, isopropylaminocarbonyl group, butylaminocarbonyl group, isobutylaminocarbonyl group, sec-butylaminocarbonyl group, tert-butylaminocarbonyl group, pentylaminocarbonyl group, isopentylaminocarbonyl group, neopentylaminocarbonyl group, 1,1-dimethylpropylaminocarbonyl group, hexylaminocarbonyl group, isohexylaminocarbonyl group, heptylaminocarbonyl group, octylaminocarbonyl group and the like. Examples of the C_1-C_8 dialkylaminocarbonyl group represented by R^2 include, for example, dimethylaminocarbonyl group, diethylaminocarbonyl group, dipropylaminocarbonyl group, diisopropylaminocarbonyl group, dibutylaminocarbonyl group, diisobutylaminocarbonyl group, dipentylaminocarbonyl group, diisopentylaminocarbonyl group, dihexylaminocarbonyl group, diisohexylaminocarbonyl group, diheptylaminocarbonyl group, dioctylaminocarbonyl group and the like. These groups may have one or more substituents A.

As the optionally substituted C_3-C_8 cycloalkyl group, optionally substituted C_3-C_8 cycloalkyloxy group, and optionally substituted C_6-C_{14} aryloxy group represented by R^2, such as those explained as to R^1 may be used. R^3 represents a pyridyl group, which may be any one of 2-pyridyl group, 3-pyridyl group, and 4-pyridyl group. The pyridyl group may have

one or more substituents B.

R^1 may preferably a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond, carbonyl group, sulfonyl group, or a nitrogen atom which may be substituted with a C_1-C_{18} alkyl group which may be substituted.

More preferably, R^1 may be a C_1-C_{18} alkyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an unsubstituted alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group, or a substituted C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond.

R^2 may preferably be hydrogen atom, a C_1-C_8 alkyl group which may be substituted, a C_3-C_8 alkenyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a halogen atom, nitro group, cyano group, an amino group which may be substituted. carboxyl group, a C_1-C_8 alkyloxycarbonyl group which may be substituted, a C_3-C_8 cycloalkyloxycarbonyl group which may be substituted, carbamoyl group, a C_1-C_8 alkylaminocarbonyl group which may be substituted, or a C_1-C_8

dialkylaminocarbonyl group which may be substituted, and more preferably, hydrogen atom, a C_1-C_8 alkyl group, or a halogen atom, and most preferably hydrogen atom. R^3 may preferably be 3-pyridyl group or 4-pyridyl group, and more preferably 4-pyridyl group.

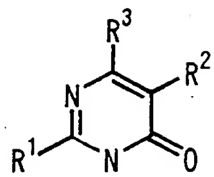
The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ-hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S)

configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers, racemates and the like fall within the scope of the present invention. Furthermore, as the pyrimidone derivatives represented by the aforementioned formula (I), a 3H-4-one compound, a 4-hydroxy compound, and a 1H-4-one compound of may exist as tautomers. The existence of such tautomers is readily apparent to those skilled in the art, and these tautomers fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in the tables below. However, the scope of the present invention is not limited by the following compounds.

Table-1



Compound No.	R^1	R^2	R^3
1	Me	H	4-Py
2	Et	H	4-Py
3	n-Pr	H	4-Py
4	i-Pr	H	4-Py
5	n-Bu	H	4-Py
6	i-Bu	H	4-Py
7	sec-Bu	H	4-Py
8	tert-Bu	H	4-Py
9	n-C_5H_{11}	H	4-Py

Table-1(continued)

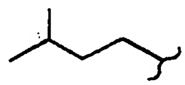
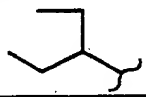
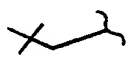
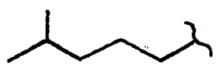
Compound No.	R^1	R^2	R^3
10		H	4-Py
11		H	4-Py
12		H	4-Py
13		H	4-Py
14	n-C_6H_{13}	H	4-Py
15		H	4-Py
16	n-C_7H_{15}	H	4-Py
17	n-C_8H_{17}	H	4-Py
18	n-C_9H_{19}	H	4-Py
19	n-$C_{10}H_{21}$	H	4-Py
20	n-$C_{11}H_{23}$	H	4-Py

Table-1(continued)

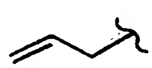
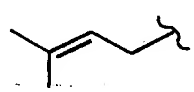
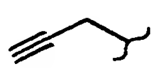
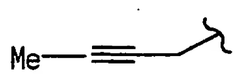
Compound No.	R^1	R^2	R^3
21	n-$C_{12}H_{25}$	H	4-Py
22	n-$C_{13}H_{27}$	H	4-Py
23	n-$C_{14}H_{29}$	H	4-Py
24	n-$C_{15}H_{31}$	H	4-Py
25	n-$C_{16}H_{33}$	H	4-Py
26	n-$C_{17}H_{35}$	H	4-Py
27	n-$C_{18}H_{37}$	H	4-Py
28		H	4-Py
29		H	4-Py
30		H	4-Py
31		H	4-Py

Table-1(continued)

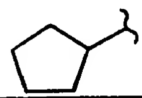
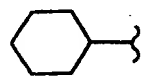
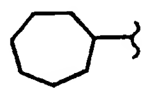
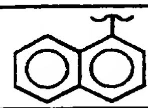
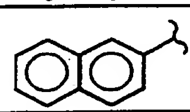
Compound No.	R^1	R^2	R^3
32		H	4-Py
33		H	4-Py
34		H	4-Py
35	Ph	H	4-Py
36		H	4-Py
37		H	4-Py
38	2-Me-Ph	H	4-Py
39	3-Me-Ph	H	4-Py
40	4-Me-Ph	H	4-Py
41	2-Et-Ph	H	4-Py
42	3-Et-Ph	H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
43	4-Et-Ph	H	4-Py
44	2-F-Ph	H	4-Py
45	3-F-Ph	H	4-Py
46	4-F-Ph	H	4-Py
47	2-Cl-Ph	H	4-Py
48	3-Cl-Ph	H	4-Py
49	4-Cl-Ph	H	4-Py
50	2-Br-Ph	H	4-Py
51	3-Br-Ph	H	4-Py
52	4-Br-Ph	H	4-Py
53	2-MeO-Ph	H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
54	3-MeO-Ph	H	4-Py
55	4-MeO-Ph	H	4-Py
56	2-EtO-Ph	H	4-Py
57	3-EtO-Ph	H	4-Py
58	4-EtO-Ph	H	4-Py
59	2-CN-Ph	H	4-Py
60	3-CN-Ph	H	4-Py
61	4-CN-Ph	H	4-Py
62	2-NO_2-Ph	H	4-Py
63	3-NO_2-Ph	H	4-Py
64	4-NO_2-Ph	H	4-Py

Table-1(continued)

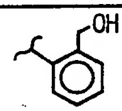
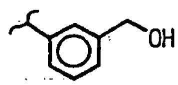
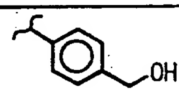
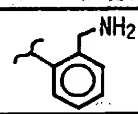
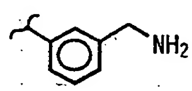
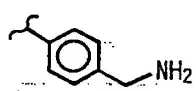
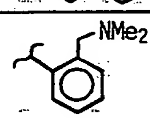
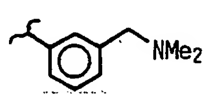
Compound No.	R^1	R^2	R^3
65	2-CF_3-Ph	H	4-Py
66	3-CF_3-Ph	H	4-Py
67	4-CF_3-Ph	H	4-Py
68		H	4-Py
69		H	4-Py
70		H	4-Py
71		H	4-Py
72		H	4-Py
73		H	4-Py
74		H	4-Py
75		H	4-Py

Table-1(continued)

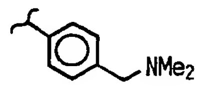
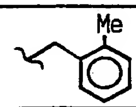
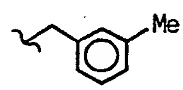
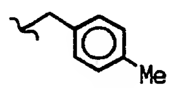
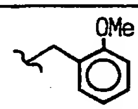
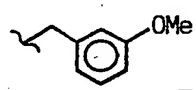
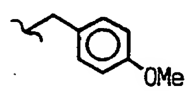
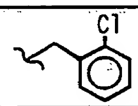
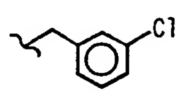
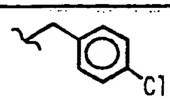
Compound No.	R^1	R^2	R^3
76		H	4-Py
77		H	4-Py
78		H	4-Py
79		H	4-Py
80		H	4-Py
81		H	4-Py
82		H	4-Py
83		H	4-Py
84		H	4-Py
85		H	4-Py
86		H	4-Py

Table-1(continued)

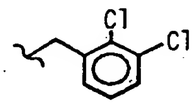
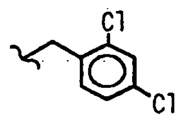
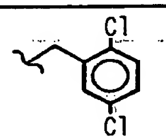
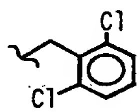
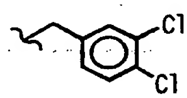
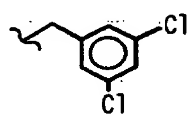
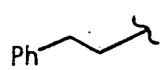
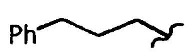
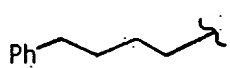
Compound No.	R^1	R^2	R^3
87		H	4-Py
88		H	4-Py
89		H	4-Py
90		H	4-Py
91		H	4-Py
92		H	4-Py
93		H	4-Py
94		H	4-Py
95		H	4-Py

Table-1(continued)

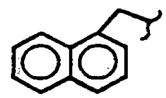
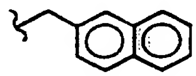
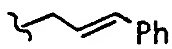
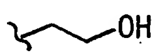
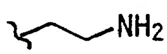
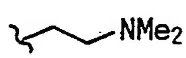
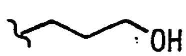
Compound No.	R^1	R^2	R^3
96		H	4-Py
97		H	4-Py
98		H	4-Py
99		H	4-Py
100		H	4-Py
101		H	4-Py
102		H	4-Py
103		H	4-Py
104		H	4-Py
105		H	4-Py
106		H	4-Py

Table-1(continued)

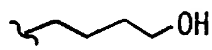
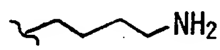
Compound No.	R^1	R^2	R^3
107		H	4-Py
108		H	4-Py
109		H	4-Py
110		H	4-Py
111		H	4-Py
112	MeO—	H	4-Py
113	EtO—	H	4-Py
114	n-PrO—	H	4-Py
115	i-PrO—	H	4-Py
116	n-BuO—	H	4-Py
117	i-BuO—	H	4-Py

Table-1(continued)

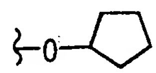
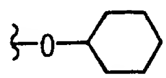
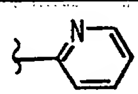
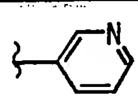
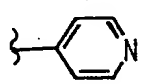
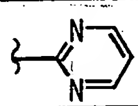
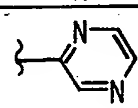
Compound No.	R^1	R^2	R^3
118	t-BuO—	H	4-Py
119	n-C_5H_{11}O—	H	4-Py
120	n-C_6H_{13}O—	H	4-Py
121		H	4-Py
122		H	4-Py
123	—OPh	H	4-Py
124		H	4-Py
125		H	4-Py
126		H	4-Py
127		H	4-Py
128		H	4-Py

Table-1(continued)

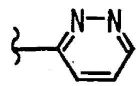
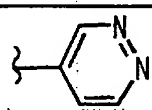
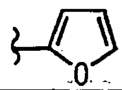
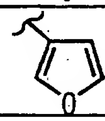
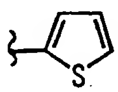
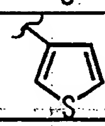
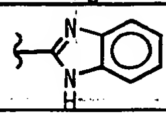
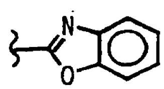
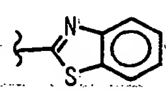
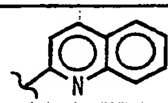
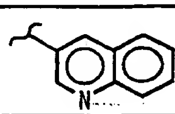
Compound No.	R^1	R^2	R^3
129		H	4-Py
130		H	4-Py
131		H	4-Py
132		H	4-Py
133		H	4-Py
134		H	4-Py
135		H	4-Py
136		H	4-Py
137		H	4-Py
138		H	4-Py
139		H	4-Py

Table-1(continued)

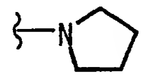
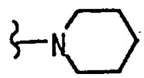
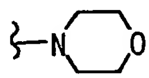
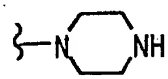
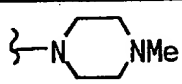
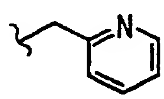
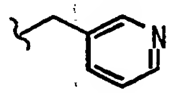
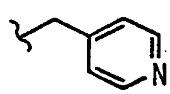
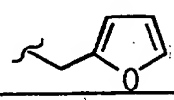
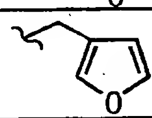
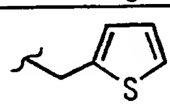
Compound No.	R^1	R^2	R^3
140		H	4-Py
141		H	4-Py
142		H	4-Py
143		H	4-Py
144		H	4-Py
145		H	4-Py
146		H	4-Py
147		H	4-Py
148		H	4-Py
149		H	4-Py
150		H	4-Py

Table-1(continued)

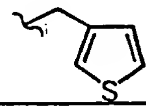
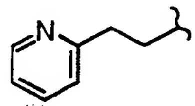
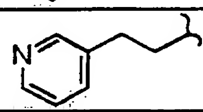
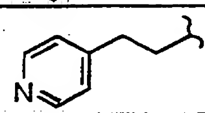
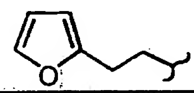
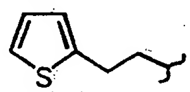
Compound No.	R^1	R^2	R^3
151		H	4-Py
152		H	4-Py
153		H	4-Py
154		H	4-Py
155		H	4-Py
156		H	4-Py
157	NH_2	H	4-Py
158	NHMe	H	4-Py
159	NHEt	H	4-Py
160	NHn-Pr	H	4-Py
161	NHi-Pr	H	4-Py

Table-1(continued)

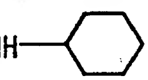
Compound No.	R^1	R^2	R^3
162	NHn-Bu	H	4-Py
163	NHi-Bu	H	4-Py
164	NHt-Bu	H	4-Py
165	NHn-C_5H_{11}	H	4-Py
166	NHn-C_6H_{13}	H	4-Py
167	NH— 	H	4-Py
168	NHPh	H	4-Py
169	NMe_2	H	4-Py
170	NEt_2	H	4-Py
171	Nn-Pr_2	H	4-Py
172	$NHNH_2$	H	4-Py

Table-1(continued)

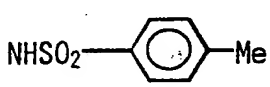
Compound No.	R^1	R^2	R^3
173	NHNHMe	H	4-Py
174	$NHNMe_2$	H	4-Py
175	$NMeNH_2$	H	4-Py
176	$NMeNMe_2$	H	4-Py
177	$NHCOCH_3$	H	4-Py
178	$NHCOC_2H_5$	H	4-Py
179	NHCOPh	H	4-Py
180	$NHSO_2Me$	H	4-Py
181	$NHSO_2Ph$	H	4-Py
182		H	4-Py
183	Ph	Me	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
184	Ph	Me	4-Py
185	Ph	Et	4-Py
186	Ph	Et	4-Py
187	Ph	n-Pr	4-Py
188	Ph	n-Pr	4-Py
189	Ph	i-Pr	4-Py
190	Ph	i-Pr	4-Py
191	Ph	n-Bu	4-Py
192	Ph	n-Bu	4-Py
193	Ph	i-Bu	4-Py
194	Ph	i-Bu	4-Py

Table-1(continued)

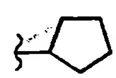
Compound No.	R^1	R^2	R^3
195	Ph	t-Bu	4-Py
196		t-Bu	4-Py
197	Ph	$n-C_5H_{11}$	4-Py
198		$n-C_5H_{11}$	4-Py
199	Ph	$n-C_6H_{13}$	4-Py
200		$n-C_6H_{13}$	4-Py
201	Ph		4-Py
202			4-Py
203	Ph		4-Py
204			4-Py
205	Ph		4-Py

Table-1(continued)

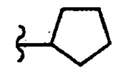
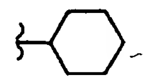
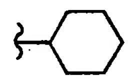
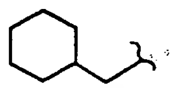
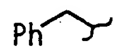
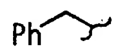
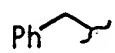
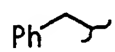
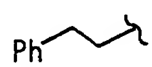
Compound No.	R^1	R^2	R^3
206			4-Py
207	Ph		4-Py
208			4-Py
209			4-Py
210			4-Py
211	Me		4-Py
212	Ph		4-Py
213			4-Py
214	Ph		4-Py
215			4-Py
216	Ph		4-Py

Table-1(continued)

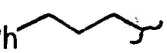
Compound No.	R^1	R^2	R^3
217	Ph	Ph	4-Py
218	Ph	OH	4-Py
219	Ph	OH	4-Py
220	Ph	OMe	4-Py
221	Ph	OMe	4-Py
222	Ph	OEt	4-Py
223	Ph	OEt	4-Py
224	Ph	OPh	4-Py
225	Ph	OPh	4-Py
226	Ph	SMe	4-Py
227	Ph	SMe	4-Py

Table-1(continued)

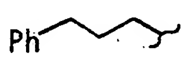
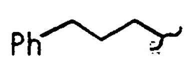
Compound No.	R^1	R^2	R^3
228	Ph	F	4-Py
229		F	4-Py
230	Ph	Cl	4-Py
231		Cl	4-Py
232	NH_2	Cl	4-Py
233	Ph	Br	4-Py
234		Br	4-Py
235	Ph	NO_2	4-Py
236		NO_2	4-Py
237	Ph	CN	4-Py
238		CN	4-Py

Table-1(continued)

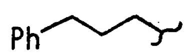
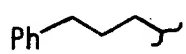
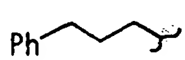
Compound No.	R^1	R^2	R^3
239	Ph	NH_2	4-Py
240		NH_2	4-Py
241	Ph	NMe_2	4-Py
242		NMe_2	4-Py
243	Ph	-COOH	4-Py
244		-COOH	4-Py
245	Ph	-COOMe	4-Py
246		-COOMe	4-Py
247	Ph	-COOEt	4-Py
248		-COOEt	4-Py
249	Ph	$CONH_2$	4-Py

Table-1(continued)

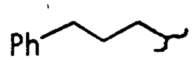
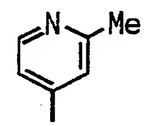
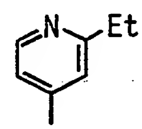
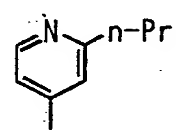
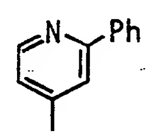
Compound No.	R^1	R^2	R^3
250		$CONH_2$	4-Py
251	Ph	$CONMe_2$	4-Py
252		$CONMe_2$	4-Py
253	Ph	H	
254		H	
255	Ph	H	
256		H	
257	Ph	H	
258		H	
259	Ph	H	
260		H	

Table-1(continued)

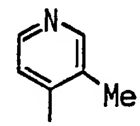
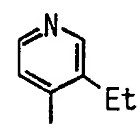
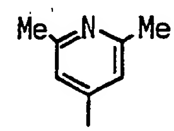
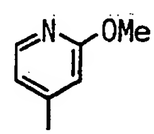
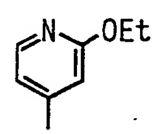
Compound No.	R^1	R^2	R^3
261	Ph	H	
262		H	
263	Ph	H	
264		H	
265	Ph	H	
266		H	
267	Ph	H	
268		H	
269	4-Py	H	
270	Ph	H	
271		H	

Table-1(continued)

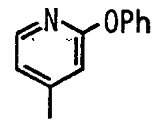
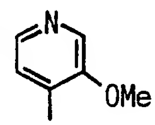
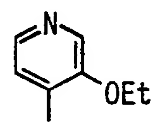
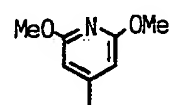
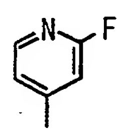
Compound No.	R^1	R^2	R^3
272	Ph	H	
273		H	
274	Ph	H	
275		H	
276	Ph	H	
277		H	
278	Ph	H	
279		H	
280	Ph	H	
281		H	

Table-1(continued)

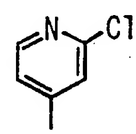
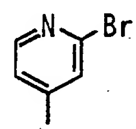
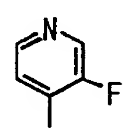
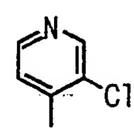
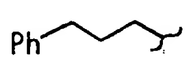
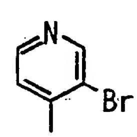
Compound No.	R^1	R^2	R^3
282	Ph	H	
283		H	
284	4-Py	H	
285	Ph	H	
286		H	
287	Ph	H	
288		H	
289	Ph	H	
290		H	
291	Ph	H	
292		H	

Table-1(continued)

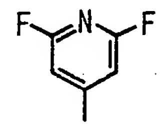
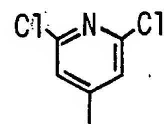
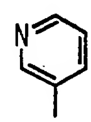
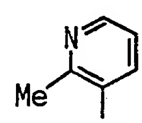
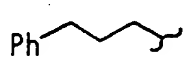
Compound No.	R^1	R^2	R^3
293	Ph	H	
294		H	
295	Ph	H	
296		H	
297	Me	H	
298	Ph	H	
299		H	
300	4-Py	H	
301	NMe_2	H	
302	Ph	H	
303		H	

Table-1(continued)

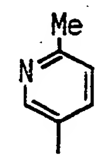
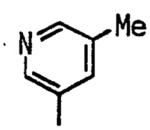
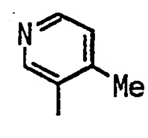
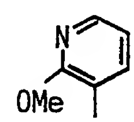
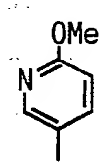
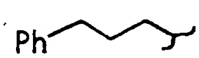
Compound No.	R^1	R^2	R^3
304	Ph	H	
305		H	
306	Ph	H	
307		H	
308	Ph	H	
309		H	
310	Ph	H	
311		H	
312	Ph	H	
313		H	

Table-1(continued)

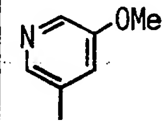
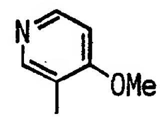
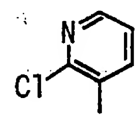
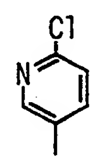
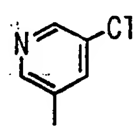
Compound No.	R^1	R^2	R^3
314	Ph	H	
315		H	
316	Ph	H	
317		H	
318	Ph	H	
319		H	
320	Ph	H	
321		H	
322	Ph	H	
323		H	

Table-1(continued)

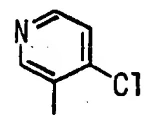
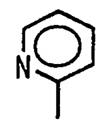
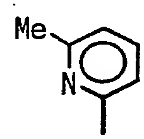
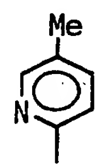
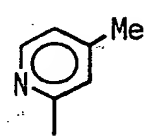
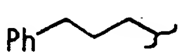
Compound No.	R^1	R^2	R^3
324	Ph	H	
325		H	
326	Ph	H	
327		H	
328	Ph	H	
329		H	
330	Ph	H	
331		H	
332	Ph	H	
333		H	

Table-1(continued)

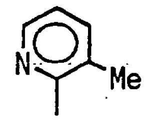
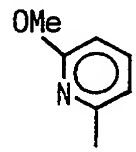
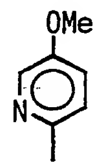
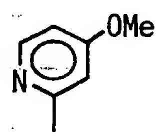
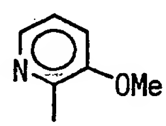
Compound No.	R^1	R^2	R^3
334	Ph	H	
335		H	
336	Ph	H	
337		H	
338	Ph	H	
339		H	
340	Ph	H	
341		H	
342	Ph	H	
343		H	

Table-1(continued)

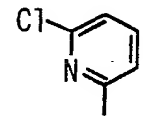
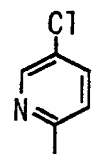
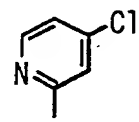
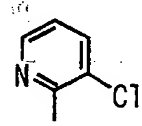
Compound No.	R^1	R^2	R^3
344	Ph	H	
345		H	
346	Ph	H	
347		H	
348	Ph	H	
349		H	
350	Ph	H	
351		H	
352	2-n-Pr-Ph	H	4-Py
353	2-i-Pr-Ph	H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
354	2-n-Bu-Ph	H	4-Py
355	2-i-Bu-Ph	H	4-Py
356	2-sec-Bu-Ph	H	4-Py
357	2-tert-Bu-Ph	H	4-Py
358	2-n-C_5H_{11}-Ph	H	4-Py
359	2-n-C_6H_{13}-Ph	H	4-Py
360	2-Ph-Ph	H	4-Py
361	3-n-Pr-Ph	H	4-Py
362	3-i-Pr-Ph	H	4-Py
363	3-n-Bu-Ph	H	4-Py
364	3-i-Bu-Ph	H	4-Py

Table-1(continued)

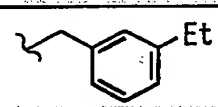
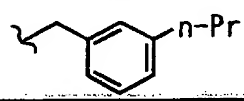
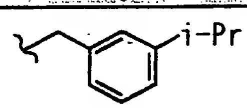
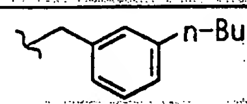
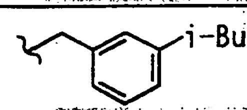
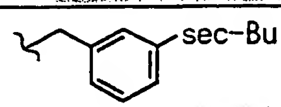
Compound No.	R^1	R^2	R^3
365	3-sec-Bu-Ph	H	4-Py
366	3-tert-Bu-Ph	H	4-Py
367	3-n-C_5H_{11}-Ph	H	4-Py
368	3-n-C_6H_{13}-Ph	H	4-Py
369	3-Ph-Ph	H	4-Py
370		H	4-Py
371		H	4-Py
372		H	4-Py
373		H	4-Py
374		H	4-Py
375		H	4-Py

Table-1(continued)

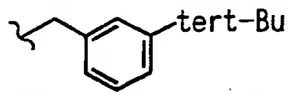
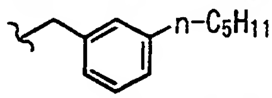
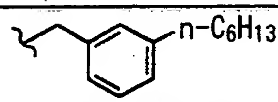
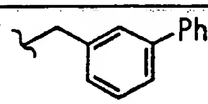
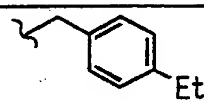
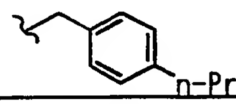
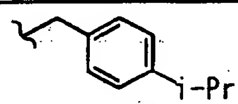
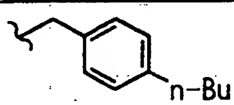
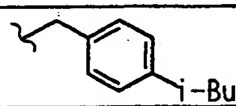
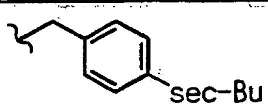
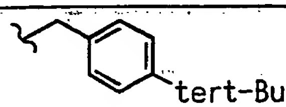
Compound No.	R^1	R^2	R^3
376		H	4-Py
377		H	4-Py
378		H	4-Py
379		H	4-Py
380		H	4-Py
381		H	4-Py
382		H	4-Py
383		H	4-Py
384		H	4-Py
385		H	4-Py
386		H	4-Py

Table-1(continued)

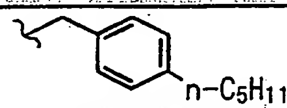
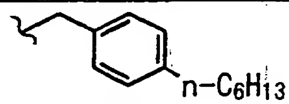
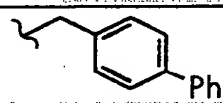
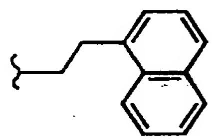
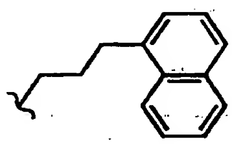
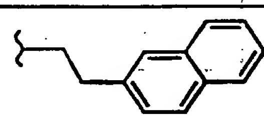
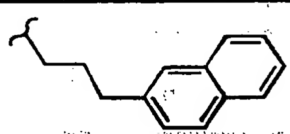
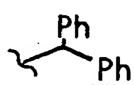
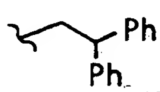
Compound No.	R^1	R^2	R^3
387		H	4-Py
388		H	4-Py
389		H	4-Py
390		H	4-Py
391		H	4-Py
392		H	4-Py
393		H	4-Py
394		H	4-Py
395		H	4-Py

Table-1(continued)

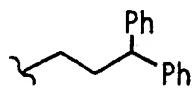
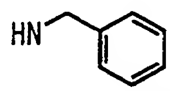
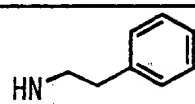
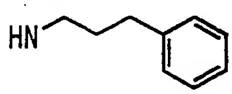
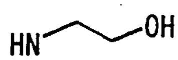
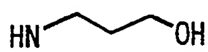
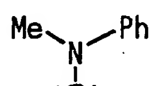
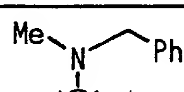
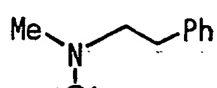
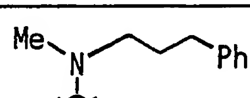
Compound No.	R^1	R^2	R^3
396		H	4-Py
397		H	4-Py
398		H	4-Py
399		H	4-Py
400		H	4-Py
401		H	4-Py
402		H	4-Py
403		H	4-Py
404		H	4-Py
405		H	4-Py
406		H	4-Py

Table-1(continued)

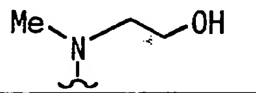
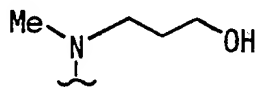
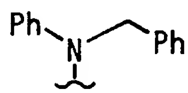
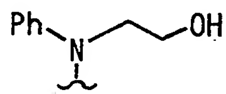
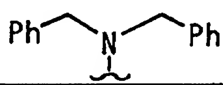
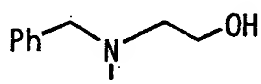
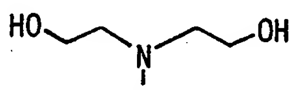
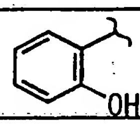
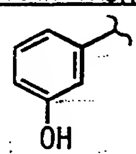
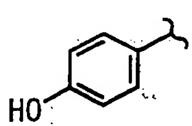
Compound No.	R^1	R^2	R^3
407		H	4-Py
408		H	4-Py
409		H	4-Py
410		H	4-Py
411		H	4-Py
412		H	4-Py
413		H	4-Py
414		H	4-Py
415		H	4-Py
416		H	4-Py

Table-1(continued)

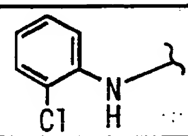
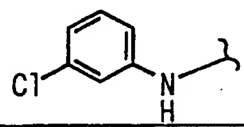
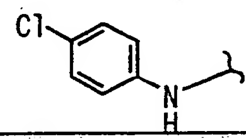
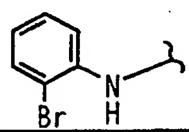
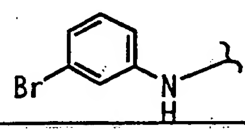
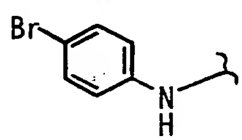
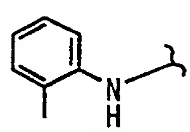
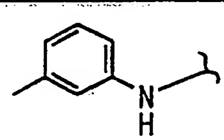
Compound No.	R^1	R^2	R^3
417		H	4-Py
418		H	4-Py
419		H	4-Py
420		H	4-Py
421		H	4-Py
422		H	4-Py
423		H	4-Py
424		H	4-Py

Table-1(continued)

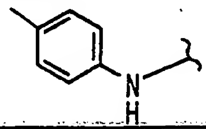
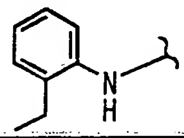
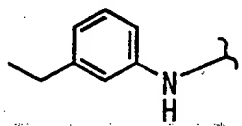
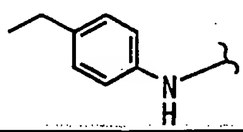
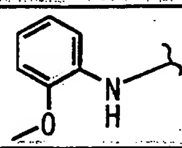
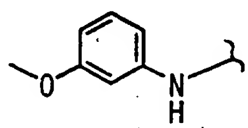
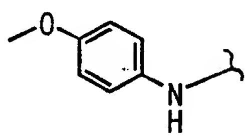
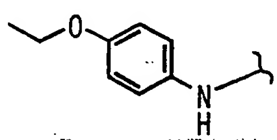
Compound No.	R^1	R^2	R^3
425		H	4-Py
426		H	4-Py
427		H	4-Py
428		H	4-Py
429		H	4-Py
430		H	4-Py
431		H	4-Py
432		H	4-Py

Table-1(continued)

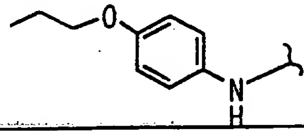
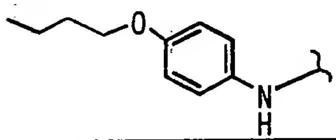
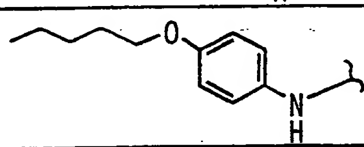
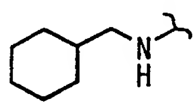
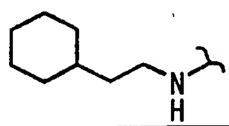
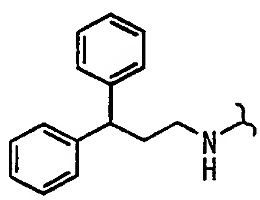
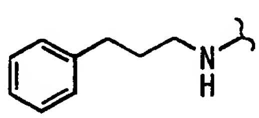
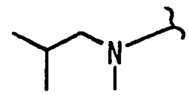
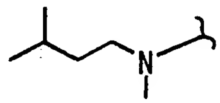
Compound No.	R^1	R^2	R^3
433		H	4-Py
434		H	4-Py
435		H	4-Py
436		H	4-Py
437		H	4-Py
438		H	4-Py
439		H	4-Py

Table-1(continued)

Compound No.	R^1	R^2	R^3
440		H	4-Py
441		H	4-Py

Particularly preferred compounds of the present invention represented by formula (I) include:

(1) compounds wherein R^2 is hydrogen atom, a C_1-C_8 alkyl group which may be substituted, a C_3-C_8 alkenyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a halogen atom, nitro group, cyano group, an amino group which may be substituted, carboxyl group, a C_1-C_8 alkyloxycarbonyl group which may be substituted, a C_3-C_8 cycloalkyloxycarbonyl group which may be substituted, carbamoyl group, a C_1-C_8 alkylaminocarbonyl group which may be substituted, or a C_1-C_8 dialkylaminocarbonyl group which may be substituted;

(2) compounds wherein R^1 is a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, a C_3-C_{18} alkenyl group which may be substituted, a C_3-C_{18} alkynyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond, carbonyl group, sulfonyl group, or a nitrogen atom which may be substituted with a C_1-C_{18} alkyl group which may be substituted;

(3) compounds wherein R^2 is hydrogen atom, a C_1-C_8 alkyl group, or a halogen atom;

(4) compounds wherein R^1 is a C_1-C_{18} alkyl group which may be substituted, a C_3-C_8 cycloalkyl group which may be substituted, a C_6-C_{14} aryl group which may be substituted, a heterocyclic group which may be substituted by an unsubstituted alkyl group, or a group represented by $-N(R^4)$-W-R^5 wherein R^4 and R^5 independently represent a hydrogen atom, a C_1-C_{18} alkyl group which may be substituted, or a C_6-C_{14} aryl group which may be substituted, and symbol "W" represents a single bond;

(5) compounds wherein R^2 is hydrogen atom;

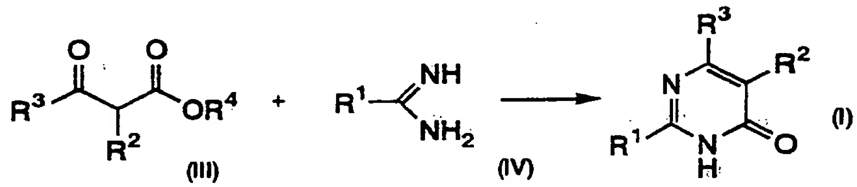
(6) compounds wherein R^3 represents a 3-pyridyl group which may be

substituted or a 4-pyridyl group which may be substituted; and

(7) compounds wherein R^3 represents a 4-pyridyl group which may be substituted.

The pyrimidone compounds represented by the aforementioned formula (I) can be prepared, for example, according to the method explained below.

<Preparation Method 1>



(In the above scheme, R^4 represents an alkyl group which may be substituted and definitions of R^1 - R^3 are the same as those already described.)

The 3-ketoester represented by the above formula(III) is allowed to react with the compound represented by formula(IV) or a salt thereof to obtain the compound of the aforementioned formula(I) in the presence of a base such as lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, 1,8-diazabicyclo[5,4,0]undec-7-en, triethylamine, diisopropylethylamine, dimethylbenzylamine, dimethylaniline, diethylaniline and the like. Compounds of formula(III) and formula(IV) are commercially available or may be synthesized according to known methods of one skilled in the art. Compound of formula(I) could be derivatised into other compound of formula(I). using well known method in the art.

Examples of a solvent include, for example. alcoholic solvent such as methanol, ethanol, 1-propanol. isopropanol. tert-butanol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene. toluene. xylene; halogenated

solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetoaminde, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used, and the reaction may be carried out for 1 minute to 14 days at a suitable temperature ranging from 0℃ to 250℃ under nitrogen or argon atmosphere or in under ordinary air. In the above reaction, protection or deprotection of a functional group may sometimes be necessary. A suitable protective group can be chosen depending on the type of a functional group, and a method described in the literature may be applied as experimental procedures.

The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in Alzheimer disease and the like, thereby suppress the neurotoxicity of Aβ and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration frontotemporal dementia and the like.

As the active ingredient of the medicament of the present invention,

a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of Alzheimer disease and the like. A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content rations of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a

daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient). and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound number in the examples corresponds to that in the table above.

Example 1: Preparation of 2-(3-pyridyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 125)

ethyl 3-(4-pyridyl)-3-oxopropionate (0.60 g), 3-amidinopyridine hydrochloride (0.54 g) and potassium carbonate (1.15 g) were added to 5 ml of ethanol, and the mixture was heated under reflux at 75 ℃ for 20 hours. Acetic acid was added to the reaction mixture, and the solvent was removed by distillation. The residue was added with water and then with acetic acid, and the resulting solid was separated by filtration. washed with water and ethyl acetate, and dried to obtain 0.39 g of the desired compound.

Yield: 50%.

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.21 (1H, s), 7.59-7.63 (1H, m), 8.16 (2H, dd, J=1.5, 4.7Hz), 8.59-8.62 (1H, m), 8.74-8.79 (3H, m), 9.41 (1H, d, J=1.8Hz).

Compounds of Example 2 to 63 were prepared in a similar manner to that in Example 1. Physical properties of the compounds are shown below.

Example 2: Preparation of 2-methyl-6-(4-pyridyl)pyrimidin-4-one (Compound 1)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.38 (3H, s), 6.94 (1H, s), 7.98 (2H, dd, J=1.9, 4.5Hz), 8.69 (2H, dd, J=1.9,4.6Hz).

Example 3: Preparation of 2-ethyl-6-(4-pyridyl)pyrimidin-4-one (Compound 2)

Melting Point: 265-269℃.

NMR (DMSO-d_6, δ): 1.26 (3H, t, J=7.5Hz), 2.65 (2H, t, J=7.5Hz), 6.93 (1H, s), 7.99 (2H, dd, J=1.8, 4.6Hz), 8.69 (2H, dd, J=1.4, 4.6Hz).

Example 4: Preparation of 2-propyl-6-(4-pyridyl)pyrimidin-4-one (Compound 3)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 0.95 (3H, t, J=7.5Hz), 1.70-1.83 (2H, m), 2.61 (2H, t, J=7.8Hz), 6.95 (1H, s), 7.99 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.8, 4.8Hz), 12.64 (1H, bs).

Example 5: Preparation of 2-isopropyl-6-(4-pyridyl)pyrimidin-4-one (Compound 4)

Melting Point: 250-252℃.

NMR (DMSO-d_6, δ): 1.27 (6H, d, J=7.2Hz), 2.86-2.95 (1H, m), 6.91 (1H, s), 8.00 (2H, dd, J=1.5, 4.2Hz), 8.70 (2H, dd, J=1.5, 4.5Hz).

Example 6: Preparation of 2-butyl-6-(4-pyridyl)pyrimidin-4-one (Compound 5)

Melting Point:282-285℃.

NMR (DMSO-d_6, δ): 0.92 (3H, t, J=7.5Hz), 1.32-1.40 (2H, m), 1.67-1.75 (2H, m), 2.63 (2H, t, J=7.5Hz), 6.94 (1H, s), 7.98 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.5, 4.2Hz), 12.59 (1H, bs).

Example 7: Preparation of 2-isobutyl-6-(4-pyridyl)pyrimidin-4-one (Compound 6)

Melting Point:280-283℃.

NMR (DMSO-d_6, δ): 0.95 (6H, d, J=6.6Hz), 2.16-2.25 (1H, m), 2.51 (2H, d, J=7.2Hz), 6.93 (1H, s), 7.98 (2H, dd, J=1.8, 4.5Hz), 8.70 (2H, dd, J=1.8, 4.5Hz), 12.59 (1H, bs).

Example 8: Preparation of 2-pentyl-6-(4-pyridyl)pyrimidin-4-one (Compound 9)

Melting Point:238-240℃.

NMR (DMSO-d_6, δ): 0.88 (3H, t, J=6.6Hz), 1.24-1.38 (4H, m), 1.78-1.90 (2H, m), 2.62 (2H, t, J=7.5Hz), 6.93 (1H, s), 7.98 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.5, 4.5Hz).

Example 9: Preparation of 2-hexyl-6-(4-pyridyl)pyrimidin-4-one (Compound 14)

Melting Point:226-229℃.

NMR (DMSO-d_6, δ): 0.86 (3H, t, J=6.9Hz), 1.21-1.38 (6H, m), 1.68-1.78 (2H, m), 2.62 (2H, t, J=7.5Hz), 6.93 (1H, s), 7.98 (2H, dd, J=1.8, 4.5Hz), 8.70 (2H,

dd, J=1.5, 4.5Hz), 12.60 (1H, bs).

Example 10: Preparation of 2-heptyl-6-(4-pyridyl)pyrimidin-4-one (Compound 16)

Melting Point: 219-220℃.

NMR (DMSO-d_6, δ): 0.85 (3H. t. J=6.8Hz), 1.19-1.37 (8H, m). 1.69-1.78 (2H, m), 2.62 (2H, t, J=7.3Hz). 6.92 (1H, s), 7.98 (2H, dd. J=1.4, 4.6Hz), 8.69 (2H, dd, J=1.9, 4.6Hz).

Example 11: Preparation of 2-octyl-6-(4-pyridyl)pyrimidin-4-one (Compound 17)

Melting Point: 197-200℃.

NMR (DMSO-d_6, δ): 0.84 (3H, t. J=6.9Hz), 1.10-1.37 (10H, m), 1.67-1.78 (2H, m), 2.61 (2H, t, J=7.5Hz), 6.89 (1H, s), 7.98 (2H, dd. J=1.8, 4.5Hz), 8.68 (2H, dd, J=1.5, 4.5Hz).

Example 12: Preparation of 2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 35)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.14 (1H. s). 7.55-7.78 (3H. m). 8.14 (2H, dd, J=1.4, 4.6Hz), 8.26-8.29 (2H, m), 8.75 (2H. dd, J=1.7, 4.6Hz).

Example 13: Preparation of 2-(1-naphthyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 36)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.20 (1H. s), 7.60-7.69 (3H. m). 7.80-7.86 (1H, m), 8.00-8.08 (3H, m). 8.10-8.18 (1H. m), 8.19-8.27 (1H. m). 8.71 (H, dd, J=1.6,

4.4Hz).

Example 14: Preparation of 6-(4-pyridyl)-2-(2-tolyl)pyrimidin-4-one (Compound 38)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.44 (3H, s), 7.12 (1H, s), 7.29-7.38 (2H, m), 7.40-7.48 (1H, m), 7.50-7.58 (1H, m), 8.03 (2H, d, J=6.3Hz), 8.71 (2H, d, J=6.0Hz), 12.90 (1H, s).

Example 15: Preparation of 6-(4-pyridyl)-2-(3-tolyl)pyrimidin-4-one (Compound 39)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.42 (3H, s), 7.11 (1H, s), 7.44-7.49 (2H, m), 8.01-8.09 (2H, m), 8.12 (2H, dd, J=1.5, 4.5Hz), 8.75 (2H, dd, J=1.5, 4.5Hz).

Example 16: Preparation of 6-(4-pyridyl)-2-(4-tolyl)pyrimidin-4-one (Compound 40)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.41 (3H, s), 7.08 (1H, s), 7.38 (2H, d, J=8.1Hz), 8.12 (2H, dd, J=1.5, 4.5Hz), 8.18 (2H, d, J=8.1Hz), 8.74 (2H, d, J=1.5, 4.8Hz).

Example 17: Preparation of 2-(4-fluorophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 46)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.06 (1H, s), 7.35-7.41 (2H, m), 8.11 (2H, dd, J=1.7, 4.5Hz), 8.36-8.39 (2H, m), 8.73 (2H, dd, J=1.6, 4.6Hz).

Example 18: Preparation of 2-(4-chlorophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 49)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.15 (1H, s), 7.63 (2H, d, J=8.7Hz), 8.13 (2H, dd, J=1.5, 4.5Hz), 8.31 (2H, d, J=8.7Hz), 8.75 (2H, d, J=6.0Hz).

Example 19: Preparation of 2-(3-bromophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 51)

Melting Point: 285-287℃.

NMR (DMSO-d_6, δ): 7.19 (1H, s), 7.52-7.57 (1H, m). 7.81-7.84 (1H, m), 8.14 (2H, dd, J=1.5, 4.5Hz), 8.28-8.32 (1H, m), 8.42-8.48 (1H, m), 8.75 (2H, dd, J=1.5, 4.8Hz).

Example 20: Preparation of 2-(3-methoxyphenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 54)

Melting Point: 262-264℃.

NMR (DMSO-d_6, δ): 3.87 (3H, s), 7.11 (1H, s), 7.16-7.20 (1H, m), 7.45-7.51 (1H, m), 7.82 (1H, s). 7.87-7.90 (1H, m), 8.12 (2H, dd. J=1.5, 4.5Hz), 8.74 (2H, dd, J=1.5, 4.5Hz).

Example 21: Preparation of 2-(3-ethoxyphenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 57)

Melting Point: 250-253℃.

NMR (DMSO-d_6, δ): 1.38 (3H, t, J=6.9Hz), 4.15 (2H, q, J=6.9Hz), 7.13 (1H, s), 7.15-7.19 (1H, m), 7.44-7.50 (1H, m), 7.80 (1H, s), 7.84-7.88 (1H, m), 8.13 (2H, dd, J=1.5, 4.8Hz). 8.75 (2H, dd, J=1.5, 4.8Hz), 12.92 (1H, bs).

Example 22: Preparation of 2-(3-cyanophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 60)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.22 (1H, s), 7.76-7.81 (1H, m), 8.07-8.10 (1H, m), 8.18 (2H, dd, J=1.2, 4.5Hz), 8.57-8.62 (1H, m), 8.71-8.77 (3H.m).

Example 23: Preparation of 2-(4-cyanophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 61)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.25 (1H, s), 8.06 (2H, d, J=8.4Hz), 8.16 (2H, dd, J=1.5, 4.5Hz), 8.47 (2H, d, J=8.4Hz), 8.76 (2H, d, J=1.5, 4.8Hz).

Example 24: Preparation of 2-(4-nitrophenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 64)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.30 (1H, s), 8.17 (2H, dd, J=1.1, 4.7Hz), 8.40 (2H, d, J=8.8Hz), 8.56 (2H, d, J=8.8Hz), 8.76 (2H, d. J=5.9Hz).

Example 25: Preparation of 6-(4-pyridyl)-2-(3-trifluorophenyl)-pyrimidin-4-one (Compound 66)

NMR (DMSO-d_6, δ): 7.18 (1H, s), 7.78-7.84 (1H, m). 7.95-8.00 (1H, m), 8.13 (2H, dd, J=1.6, 4.5Hz), 8.60-8.63 (2H, m), 8.76 (2H, dd. J=1.6, 4.5Hz).

Example 26: Preparation of 6-(4-pyridyl)-2-(4-trifluorophenyl)-pyrimidin-4-one (Compound 67)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.26 (1H, s). 7.95 (2H. d, J=8.4Hz). 8.15 (2H. dd, J=1.2,

4.8Hz), 8.50 (2H, d, J=8.1Hz), 8.77 (2H, dd, J=0.9, 4.8Hz), 13.09 (1H, bs).

Example 27: Preparation of 2-(3-(dimethylaminomethyl)phenyl)-6-(4-pyridyl)-pyrimidin-4-one dihydrochloride (Compound 75)

Melting Point: 185-190℃.

NMR (DMSO-d_6, δ): 2.75 (6H, d, J=4.8Hz), 4.40 (2H, d, J=5.1Hz), 7.36 (1H, s), 7.68 (1H, t, J=7.8Hz), 7.85 (1H, d, J=7.8Hz), 8.33 (1H, d, J=7.8Hz), 8.51 (1H, s), 8.59 (2H, d, J=6.6Hz), 8.94 (2H, d, J=6.3Hz), 10.98 (1H,bs).

Example 28: Preparation of 2-benzyl-6-(4-pyridyl)pyrimidin-4-one (Compound 77)

Melting Point: 290-294℃.

NMR (DMSO-d_6, δ): 3.96 (2H, s), 6.97 (1H, s), 7.26-7.42 (5H, m), 7.96 (2H, dd, J=1.5, 4.8Hz), 8.69 (2H, dd, J=1.5, 4.5Hz), 12.87 (1H,bs).

Example 29: Preparation of 2-(2-methylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 78)

Melting Point: 260-263℃.

NMR (DMSO-d_6, δ): 2.39 (3H, s), 3.99 (2H, s), 6.98 (1H, s), 7.10-7.20 (3H, m), 7.21-7.29 (1H, m), 7.89 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 12.83 (1H, bs).

Example 30: Preparation of 2-(3-methylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 79)

Melting Point: 245-247℃.

NMR (DMSO-d_6, δ): 2.29 (3H, s), 3.92 (2H, s), 6.97 (1H, s), 7.05-7.09 (1H, m), 7.17-7.26 (3H, m), 7.96 (2H, dd, J=1.8, 4.5Hz), 8.69 (2H, dd, J=1.5, 4.5Hz),

12.85 (1H, bs).

Example 31: Preparation of 2-(4-methylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 80)

Melting Point: 267-270℃.

NMR (DMSO-d_6, δ): 2.26 (3H, s), 3.91 (2H, s), 6.96 (1H, s), 7.14 (2H, d, J=7.9Hz), 7.29 (2H, d. J=8.1Hz), 7.96 (2H, dd, J=1.5. 4.6Hz), 8.69 (2H, dd, J=1.8, 4.6Hz).

Example 32: Preparation of 2-(4-methoxybenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 83)

Melting Point: 255-257℃.

NMR (DMSO-d_6, δ): 3.72 (3H, s), 3.88 (2H, s), 6.90 (2H, d, J=11.7Hz), 6.95 (1H, s), 7.32 (2H, d, J=11.7Hz), 7.96 (2H, dd, J=1.5, 4.5Hz), 8.69 (2H, dd, J=1.5, 4.8Hz), 12.83 (1H, bs).

Example 33: Preparation of 2-(4-chlorobenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 86)

Melting Point: 277-280℃.

NMR (DMSO-d_6, δ): 3.97 (2H, s), 6.96 (1H, s), 7.37-7.41 (1H, m), 7.94 (2H, dd, J=1.6, 4.4Hz), 8.68 (2H, dd, J=1.6, 4.5Hz).

Example 34: Preparation of 2-(2,4-dichlorobenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 88)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 4.14 (2H. s), 7.00 (1H, s), 7.44-7.52 (2H, m), 7.66 (1H, d, J=2.1Hz), 7.80 (2H. dd, J=1.5. 4.5Hz), 8.65 (2H. dd. J=1.5. 4.5Hz). 12.91 (1H,

bs).

Example 35: Preparation of 2-(2-phenylethyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 93)

Melting Point: 264-266℃.

NMR (DMSO-d_6, δ): 2.91-2.97 (2H, m), 3.06-3.11 (2H, m), 6.95 (1H, s), 7.17-7.22 (1H, m), 7.25-7.33 (4H, m), 8.00 (2H, dd, J=1.5, 4.5Hz), 8.70 (2H, dd, J=1.5, 4.8Hz).

Example 36: Preparation of 2-(3-phenylpropyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 94)

Melting Point: 238-248℃.

NMR (DMSO-d_6, δ): 2.01-2.11 (2H, m), 2.63-2.70 (4H, m), 6.94 (1H, s), 7.16-7.32 (4H, m), 7.99 (2H, dd, J=1.5, 4.8Hz), 8.70 (2H, dd, J=1.5, 4.8Hz), 12.60 (1H, bs).

Example 37: Preparation of 2-(2-pyridyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 124)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.22 (1H, s), 7.66-7.71 (1H, m), 8.08-8.18 (3H, m), 8.54-8.59 (1H, m), 8.75-8.80 (3H,m).

Example 38: Preparation of 2.6-di(4-pyridyl)pyrimidin-4-one (Compound 126)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.29 (1H, s), 8.17 (2H, dd, J=1.4, 4.6Hz), 8.22 (2H, d, J=6.2Hz), 8.76 (2H, d, J=6.2Hz), 8.82 (2H, dd, J=1.6, 4.6Hz).

Example 39: Preparation of 2-(2-pyrazinyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 128)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 6.73 (1H, s), 8.05 (2H, dd, J=1.4. 4.7Hz), 8.65-8.74 (4H, m), 9.52 (1H, s).

Example 40: Preparation of 6-(4-pyridyl)-2-(2-pyridylmethyl)pyrimidin-4-one (Compound1 45)

Melting Point: 249-252℃.

NMR (DMSO-d_6, δ): 4.19 (2H, s), 7.00 (1H, s), 7.25-7.33 (1H, m), 7.41-7.49 (1H, m), 7.77-7.82 (1H, m), 7.90 (2H, dd, J=1.5, 4.5Hz), 8.48-8.51 (1H, m), 8.67 (2H, dd, J=1.5, 4.8Hz), 12.84 (1H, bs).

Example 41: Preparation of 6-(4-pyridyl)-2-(3-pyridylmethyl)pyrimidin-4-one (Compound 146)

Melting Point: 267-269℃.

NMR (DMSO-d_6, δ): 4.01 (2H, s), 6.94 (1H, s), 7.36-7.42 (1H, m), 7.80-7.85 (1H, m), 7.91 (2H, dd, J=1.7, 4.6Hz), 8.46-8.50 (1H. m), 8.59-8.62 (1H. m), 8.67 (2H, dd, J=1.4, 4.6Hz).

Example 42: Preparation of 6-(4-pyridyl)-2-(2-thienylmethyl)pyrimidin-4-one (Compound 150)

Melting Point: 268-270℃.

NMR (DMSO-d_6, δ): 4.19 (2H, s), 6.98-7.01 (2H, m). 6.99 (1H, s), 7.06-7.07 (1H, m), 7.44 (1H, dd, J=1.2, 5.2Hz), 7.99 (2H, dd. J=1.5. 4.6Hz), 8.71 (2H, dd, J=1.7, 4.6Hz).

Example 43: Preparation of 2-amino-6-(4-pyridyl)pyrimidin-4-one (Compound 157)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 6.28 (1H. s). 6.73 (2H, bs), 7.87 (2H, dd, J=1.5, 4.8Hz), 8.64 (2H, dd, J=1.5, 4.8Hz), 10.99 (1H, bs).

Example 44: Preparation of 2-dimethylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 169)

Melting Point: >240℃.

NMR (DMSO-d_6, δ): 3.14 (6H. s). 6.31 (1H, s), 7.94 (2H, dd, J=1.5, 4.8Hz), 8.67 (2H, dd, J=1.5, 4.8Hz).

Example 45: Preparation of 5-methyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 183)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 2.06 (3H,s), 7.49-7.59 (3H, m), 7.64 (2H, dd, J=1.5, 4.5Hz), 8.12-8.15 (2H, m), 8.72 (2H, dd, J=1.5, 4.5Hz). 12.93 (1H, bs).

Example 46: Preparation of 5-methyl-2-(3-phenylpropyl)-6-(4-pyridyl) pyrimidin-4-one (Compound 184)

Melting Point: 141-143℃.

NMR (DMSO-d_6, δ): 1.93-2.03 (2H, m), 1.95 (3H, s), 2.55-2.66 (4H, m), 7.14-7.30 (5H, m), 7.51 (2H, dd. J=1.5, 4.5Hz), 8.68 (2H. dd, J=1.5, 4.2Hz). 12.50 (1H. bs).

Example 47: Preparation of 5-ethyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 185)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 1.09 (3H, t, J=7.5Hz), 2.42 (2H, q, J=7.5Hz), 7.48-7.59 (5H, m), 8.09-8.12 (2H, m), 8.72 (2H, dd, J=1.5, 4.2Hz), 12.87 (1H, bs).

Example 48: Preparation of 5-ethyl-2-(3-phenylpropyl)-6-(4-pyridyl) pyrimidin-4-one (Compound 186)

Melting Point: 161-163℃.

NMR (DMSO-d_6, δ): 1.02 (3H, t, J=7.5Hz), 1.89-2.01 (2H, m), 2.31 (2H, q, J=7.5Hz), 2.54-2.66 (4H, m), 7.14-7.29 (5H, m), 7.43 (2H, dd, J=1.2, 4.5Hz), 8.67 (2H, d, J=1.5, 4.8Hz), 12.50 (1H, bs).

Example 49: Preparation of 2-phenyl-5-propyl-6-(4-pyridyl)pyrimidin-4-one (Compound 187)

Melting Point: 274-275℃.

NMR (DMSO-d_6, δ): 0.81 (3H, t, J=7.5Hz), 1.49 (2H, m), 2.39 (2H, t, J=7.5Hz), 7.48-7.60 (5H, m), 8.10 (2H, d, J=7.2Hz), 8.72 (2H, dd, J=1.5, 4.5Hz), 12.91 (1H, bs).

Example 50: Preparation of 2-(3-phenylpropyl)-5-propyl-6-(4-pyridyl) pyrimidin-4-one (Compound 188)

Melting Point: 148-149℃.

NMR (DMSO-d_6, δ): 0.76 (3H, t, J=7.5Hz), 1.14 (2H, m), 1.96 (2H, m), 2.27 (2H, t, J=7.8Hz), 2.51-2.65 (4H, m), 7.13-7.20 (3H, m), 7.24-7.29 (2H, m), 7.41 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 12.51 (1H, bs).

Example 51: Preparation of 5-butyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 191)

Melting Point: 269-270℃.

NMR (DMSO-d_6, δ): 0.78 (3H, t, J=7.5Hz), 1.21 (2H. m), 1.46 (2H, m), 2.42 (2H, t, J=8.7Hz), 7.48-7.60 (5H, m), 8.11 (2H, d, J=7.2Hz), 8.71 (2H, dd, J=1.5, 4.5Hz).

Example 52: Preparation of 5-butyl-2-(3-phenylpropyl)-6-(4-pyridyl) pyrimidin-4-one (Compound 192)

Melting Point: 146-147℃.

NMR (DMSO-d_6, δ): 0.75 (3H, t, J=7.2Hz), 1.17 (2H. m), 1.40 (2H, m), 1.96 (2H, m), 2.49 (2H, t, J=7.2Hz), 2.50-2.65 (4H, m), 7.13-7.20 (3H, m), 7.24-7.29 (2H, m), 7.42 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 12.51 (1H, bs).

Example 53: Preparation of 5-benzyl-2-methyl-6-(4-pyridyl)pyrimidin-4-one (Compound 211)

NMR (DMSO-d_6, δ): 2.33 (3H, s), 3.73 (2H, s), 6.91-6.99 (2H, m), 7.11-7.29 (3H, m), 7.35 (2H, d, J=4.5Hz), 7.62 (2H, d, J=5.7Hz). 12.68 (1H, bs).

Example 54: Preparation of 5-benzyl-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 212)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.04-7.07 (2H, m), 7.15-7.26 (3H, m), 7.48-7.59 (5H, m), 8.13-8.16 (2H, m), 8.67 (2H, d, J=4.8Hz), 13.02 (1H, bs).

Example 55: Preparation of 6-(2-ethylpyridin-4-yl)-2-(3-phenylpropyl) pyrimidin-4-one (Compound 256)

Melting Point: 139-141℃.

NMR (DMSO-d_6, δ): 1.26 (3H, t, J=7.5Hz), 2.06 (2H, m), 2.63-2.70 (4H, m), 2.82 (2H, q, J=7.5Hz), 6.90 (1H, s), 7.18-7.30 (5H, m), 7.78 (1H, d, J=6.9Hz), 7.84 (1H, s), 8.58 (1H, d, J=5.1Hz).

Example 56: Preparation of 6-(2-methoxypyridin-4-yl)-2-(3-phenylpropyl) pyrimidin-4-one (Compound 268)

Melting Point: 179-181℃.

NMR (DMSO-d_6, δ): 2.09 (2H, m), 2.62-2.67 (4H, m), 3.89 (3H, s), 6.89 (1H, s), 7.12-7.38 (5H, m), 7.41 (1H, s), 8.27 (1H, d, J=5.4Hz), 12.55 (1H, bs).

Example 57: Preparation of 6-(2-methoxypyridin-4-yl)-2-(4-pyridyl)pyrimidin-4-one (Compound 269)

Melting Point: 273-274℃.

NMR (DMSO-d_6, δ): 3.93 (3H, s), 7.24 (1H, bs), 7.58 (1H, s), 7.74 (1H, d, J=5.4Hz), 8.20 (2H, d, J=6.0Hz), 8.33 (2H, d, J=5.4Hz), 8.80 (2H, dd, J=1.5, 4.5Hz).

Example 58: Preparation of 6-(2-chloropyridin-4-yl)-2-(3-phenylpropyl)-pyrimidin-4-one (Compound 283)

Melting Point: 177-179℃.

NMR (DMSO-d_6, δ): 2.06 (2H, m), 2.63-2.70 (4H, m), 7.02 (1H, s), 7.18-7.31 (5H, m), 8.02 (1H, dd, J=1.5, 5.1Hz), 8.08 (1H, d, J=1.5Hz), 8.53 (1H, d, J=5.1Hz), 12.63 (1H, bs).

Example 59: Preparation of 6-(2-chloropyridin-4-yl)-2-(4-pyridyl)pyrimidin-4-one (Compound 284)

Melting Point: 179-181℃.

NMR (DMSO-d_6, δ): 7.35 (1H. bs). 8.19-8.23 (3H. m). 8.27 (1H. s), 8.59 (1H, d, J=4.8Hz), 8.81 (2H, dd. J=1.5, 4.5Hz).

Example 60: Preparation of 2-methyl-6-(3-pyridyl)pyrimidin-4-one (Compound 297)

Melting Point: 261-263℃.

NMR (DMSO-d_6, δ): 2.38 (3H, s), 6.87 (1H, s), 7.43-7.53 (1H, m), 8.36-8.40 (1H, m), 8.65-8.67 (1H. m), 9.20 (1H, d, J=2.1Hz), 12.57 (1H, bs).

Example 61: Preparation of 2-phenyl-6-(3-pyridyl)pyrimidin-4-one (Compound 298)

Melting Point: 233-236℃.

NMR (DMSO-d_6, δ): 7.05 (1H, s), 7.54-7.60 (4H, m), 8.26-8.30 (2H, m), 8.52-8.55 (1H, m), 8.69-8.72 (1H, m), 9.36 (1H, d, J=2.1Hz).

Example 62: Preparation of 6-(3-pyridyl)-2-(4-pyridyl)pyrimidin-4-one (Compound 300)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.23 (1H, s), 7.55-7.59 (1H, m). 8.23 (2H. dd, J=1.2, 4.5Hz). 8.56-8.60 (1H. m), 8.71-8.74 (1H, m). 8.81 (2H, d, J=1.5. 4.8Hz), 9.39 (1H, d, J=2.1Hz), 13.03 (1H, bs).

Example 63: Preparation of 2-dimethylamino-6-(3-pyridyl)pyrimidin-4-one (Compound 301)

Melting Point: 263-266℃.

NMR (DMSO-d_6, δ): 3.14 (6H, s), 6.25 (1H, bs). 7.45-7.50 (1H, m), 8.34-8.37 (1H, m), 8.62-8.65 (1H. m), 9.19 (1H, d, J=1.8Hz).

Example 64: Preparation of 5-bromo-2-phenyl6-(4-pyridyl)pyrimidin-4-one (Compound 233)

2-Phenyl-6-(4-pyridyl)pyrimidin-4-one (0.61 g) obtained in Example 12 was dissolved in 3 ml of acetic acid, and then the mixture was added with 0.48 g of N-bromosuccinimide and heated at 90℃ for 1 hour. Water was added to the reaction mixture, and solid mass was separated by filtration. The solid was washed with water, acetone, and ethyl acetate, and dried to obtain 0.74 g of the desired compound.

Yield: 93%.

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.51-7.65 (3H, m), 7.73 (2H, dd, J=1.5, 4.5Hz), 8.13 (2H, d, J=7.2Hz), 8.75 (2H, dd, J=1.5, 4.5Hz), 13.45 (1H, bs).

Compounds of Example 65 to 98 were prepared in a similar manner to that in Example 1. Physical properties of the compounds are shown below.

Example 65: Preparation of 5-chloro-2-phenyl-6-(4-pyridyl)pyrimidin-4-one (Compound 230)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 7.52-7.62 (3H, m), 7.79 (2H, dd, J=1.5, 4.5Hz), 8.12-8.16 (2H, m), 8.77 (2H, dd, J=1.5, 4.5Hz), 13.51 (1H, bs).

Example 66: Preparation of 2-amino-5-chloro-6-(4-pyridyl)pyrimidin-4-one (Compound 232)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 6.86 (2H, bs), 7.56 (2H, dd, J=1.5, 4.5Hz), 8.67 (2H, dd, J=1.5, 4.5Hz), 11.59 (1H, bs).

Example 67: Preparation of 2-benzoylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 179)

Melting Point: 257-259°C.

NMR (DMSO-d_6, δ): 7.25 (1H, bs), 7.29 (1H, s), 7.62-7.67 (2H, m), 7.80 (1H, t, J=7.5Hz), 8.02 (2H, dd, J=1.8, 4.5Hz), 8.12-8.15 (2H, m), 8.75 (2H, dd, J=1.8, 4.5Hz).

Example 68: Preparation of 2-(2-chlorobenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 84)

Melting Point: 264-266°C.

NMR (DMSO-d_6, δ): 4.14 (2H, s), 7.00 (1H, s), 7.31-7.50 (4H, m), 7.81 (2H, d, J=6.0Hz), 8.64 (2H, d, J=5.7Hz), 12.91(1H, bs).

Example 69: Preparation of 2-(1-piperidino)-6-(4-pyridyl)pyrimidin-4-one (Compound 141)

Melting Point:267-268°C.

NMR (DMSO-d_6, δ): 1.50-1.59 (6H, m), 3.67 (4H, m). 6.29 (1H, s), 7.89 (2H, d, J=5.7Hz), 8.62 (2H, d, J=5.7Hz).

Example 70: Preparation of 2-(4-methyl-1-piperazino)-6-(4-pyridyl)pyrimidin-4-one (Compound 144)

Melting Point: 275°C, decomposition.

NMR (DMSO-d_6, δ): 2.77, 2.79 (3H, s), 3.00-3.20 (2H, m), 3.40-3.58 (4H, m), 4.62-4.78 (2H, m), 6.80 (1H, br), 8.45 (2H, d, J=6.6Hz), 8.92 (2H, d, J=6.6Hz),

11.28 (1H, br).

Example 71: Preparation of 2-(diethylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 170)

Melting Point: 199-200℃.

NMR (DMSO-d_6, δ): 1.15 (6H, t, J=7.0Hz), 3.60 (4H, q, J=7.0Hz), 6.32 (1H, s), 7.93 (2H, d, J=5.8Hz), 8.67 (2H, d, J=5.7Hz).

Example 72: Preparation of 6-(4-chloro-3-pyridyl)-2-phenylpyrimidin-4-one (Compound 320)

Melting Point: 286-288℃.

NMR (DMSO-d_6, δ): 7.09 (1H, s), 7.54-7.69 (4H, m), 8.25-8.28 (2H, m), 8.60 (1H, dd, J=2.5, 8.4Hz), 9.19 (1H, d, J=2.3Hz).

Example 73: Preparation of 6-(4-chloro-3-pyridyl)-2-(3-phenylpropyl) pyrimidin-4-one (Compound 321)

Melting Point: 194-196℃.

NMR (DMSO-d_6, δ): 2.01-2.11 (2H, m), 2.62-2.69 (4H, m), 6.89 (1H, s), 7.15-7.31 (5H, m), 7.63 (1H, d, J=8.3Hz), 8.44 (1H, dd, J=2.5, 8.4Hz), 9.05 (1H, d, J=2.3Hz).

Example 74: Preparation of 2-phenyl-6-(2-pyridyl)pyrimidin-4-one (Compound 326)

Melting Point: 268-271℃.

NMR (DMSO-d_6, δ): 7.22 (1H, s), 7.51-7.61 (4H, m), 7.97-8.03 (1H, m), 8.28-8.36 (2H, m), 8.49 (1H, d, J=7.5Hz), 8.73 (1H, d, J=4.2Hz).

Example 75: Preparation of 2-(3-phenylpropyl)-6-(2-pyridyl)pyrimidin-4-one (Compound 327)

Melting Point: 168-170℃.

NMR (DMSO-d_6, δ): 2.03-2.13 (2H, m), 2.64-2.71 (4H, m), 7.06 (1H, s), 7.17-7.33 (5H, m), 7.49-7.53 (1H, m), 7.94-8.00 (1H, m), 8.29 (1H, d, J=8.1Hz), 8.69 (1H, d, J=3.9Hz), 12.55 (1H, bs).

Example 76: Preparation of 2-(3-biphenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 369)

Melting Point: 296-298℃.

NMR (DMSO-d_6, δ): 7.10 (1H, s), 7.40-7.47 (1H, m), 7.51-7.56 (2H, m), 7.62-7.70 (1H, m), 7.82-7.85 (2H, m), 7.90-7.93 (1H, m), 8.14 (2H, d, J=5.8Hz), 8.29-8.34 (1H, m), 8.53 (1H, s), 8.74 (2H, d, J=5.8Hz).

Example 77: Preparation of 2-(4-propylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 381)

Melting Point: 249-252℃.

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=6.9Hz), 1.52-1.59 (2H, m), 2.52 (2H, t, J=7.2Hz), 3.91 (2H s), 6.97 (1H, s), 7.15 (2H, d, J=8.1Hz), 7.30 (2H, d, J=8.1Hz), 7.97 (2H, d, J=6.3Hz), 8.69 (2H, d, J=6.0Hz), 12.86 (1H, bs).

Example 78: Preparation of 2-(4-butylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 383)

Melting Point: 241-243℃.

NMR (DMSO-d_6, δ): 0.87 (3H, t, J=7.2Hz), 1.24-1.31 (2H, m), 1.47-1.57 (2H, m), 2.53 (2H, t, J=7.5Hz), 3.91 (2H, s), 6.96 (1H, s), 7.15 (2H, d, J=8.1Hz), 7.30 (2H, d, J=7.8Hz), 7.96 (2H, d, J=5.7Hz), 8.69 (2H, d, J=5.7Hz), 12.85

(1H. bs).

Example 79: Preparation of 2-(N-benzyl-N-methylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 404)

Melting Point: 223-224℃.

NMR (DMSO-d_6, δ): 3.11 (3H, s), 4.92 (2H, s), 6.40 (1H, s), 7.24-7.38 (5H, m), 7.95 (2H, d, J=5.7Hz), 8.66 (2H, d, J=5.7Hz), 11.36 (1H, bs).

Example 80: Preparation of 2-benzylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 397)

Melting Point: 230-232℃.

NMR (DMSO-d_6, δ): 4.61 (d, J=5.7Hz, 2H), 6.34 (s, 1H), 7.12 (br, 1H), 7.23-7.41 (m, 5H), 7.90 (dd, J=1.5Hz, 4.5Hz, 2H), 8.65 (dd, J=1.5Hz, 4.5Hz, 2H), 11.02 (br, 1H).

Example 81: Preparation of 2-(3,3-diphenylpropylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 438)

Melting Point: 227-228℃.

NMR (DMSO-d_6, δ): 2.33(m, 2H), 4.04 (t, J=7.5Hz, 2H). 6.28 (s, 1H). 6.70 (br, 1H), 7.16-7.36 (m, 10H), 7.77 (d, J=6.0Hz, 2H), 8.64 (dd, J=1.2Hz, 6.0Hz, 2H), 10.93 (br, 1H).

Example 82: Preparation of 2-(4-morpholinyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 142)

Melting Point: 285-288℃.

NMR (DMSO-d_6, δ): 3.70(m. 8H). 6.44 (br, 1H), 7.95 (d. J=6.0Hz. 2H). 8.66 (dd. J=1.5Hz. 6.0Hz. 2H). 11.44 (br. 1H).

Example 83: Preparation of 2-cyclohexyl-6-(4-pyridyl)pyrimidin-4-one (Compound 33)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 1.20-1.40 (m, 3H), 1.55-1.75 (m, 3H), 1.78-1.93 (m, 4H), 2.63 (m, 1H), 2.92 (s, 1H), 7.99 (dd, J=1.5Hz, 4.8Hz. 2H), 8.70 (dd, J=1.Hz, 4.8Hz, 2H), 12.49 (br, 1H).

Example 84: Preparation of 2-(N-isobutyl-N-methylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 440)

Melting Point: 212-213℃.

NMR (DMSO-d_6, δ):0.89(d, J=6.6Hz, 6H), 2.06(m, 1H), 3.12(s, 3H), 3.46(d, J=7.2Hz, 2H), 6.29(br, 1H), 7.93(d, J=6.0Hz, 2H), 8.67(dd, J=1.5Hz, 6.0Hz, 2H), 11.10(br, 1H).

Example 85: Preparation of 2-dipropylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 171)

Melting Point: 208-209℃.

NMR(DMSO-d_6, δ): 0.90 (t, J=7.5Hz, 6H), 1.60 (m, 4H), 3.50 (t, J=7.5Hz, 4H), 6.30 (br, 1H), 7.92 (d, J=6.0Hz, 2H), 8.67 (d, J=6.0Hz. 2H), 11.20 (br, 1H).

Example 86: Preparation of 2-(3-hydroxypropylamino)-6-(4-pyridyl)pyrimidin -4-one (Compound 401)

Melting Point: 217-219℃.

NMR (DMSO-d_6, δ): 1.73 (m, 2H), 3.44-3.53 (m, 4H). 4.59 (t, J=5.1Hz. 1H), 6.31 (s, 1H), 6.64 (br, 1H), 7.93 (dd, J=1.5Hz, 6.0Hz. 2H), 8.66 (dd, J=1.5Hz, 6.0Hz, 2H), 10.94 (br, 1H).

Example 87: Preparation of 2-(1-pyrrolidinyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 140)

Melting Point: >300℃.

NMR (DMSO-d_6, δ): 1.92 (m. 4H), 3.53 (m, 4H), 6.28 (brs, 1H), 7.94 (dd, J=1.5Hz, 6.0Hz, 2H), 8.66 (dd. J=1.5Hz, 6.0Hz, 2H), 11.14 (br, 1H).

Example 88: Preparation of 2-cyclohexylmethylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 436)

Melting Point: 203-205℃.

NMR (DMSO-d_6, δ): 0.80-1.05 (m, 2H), 1.05-1.35 (m. 3H), 1.55-1.80 (m, 6H), 3.25 (m, 2H), 6.30 (s, 1H), 6.65 (br, 1H), 7.91 (dd, J=1.5Hz, 4.5Hz, 2H), 8.66 (dd, J=1.5Hz, 4.5Hz, 2H), 10.78 (br, 1H).

Example 89: Preparation of 2-(ethylphenylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 428)

Melting Point: 232-235℃.

NMR (DMSO-d_6, δ): 1.19 (t, J=7.5Hz, 3H), 2.59 (q, J=7.5Hz, 2H). 6.58 (s, 1H), 7.23 (d, J=8.4Hz, 2H). 7.60 (d, J=8.4Hz, 2H), 7.95 (d. J=6.0Hz. 2H), 8.71 (dd, J=1.2Hz, 6.0Hz, 2H), 8.89 (br, 1H), 10.91 (br, 1H).

Example 90: Preparation of 2-(butoxyphenylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 434)

Melting Point: 207-209℃.

NMR (DMSO-d_6, δ): 0.94 (t, J=7.5Hz, 3H), 1.42 (m. 2H), 1.70 (m, 2H), 3.96 (t, J=6.6Hz, 2H), 6.54 (s. 1H), 6.95 (d, J=9.0Hz, 2H). 7.56 (d, J=9.0Hz, 2H), 7.92 (d. J=6.0Hz, 2H), 8.69 (d. J=6.0Hz, 2H), 8.85 (br, 1H). 10.93 (br, 1H).

Example 91: Preparation of 2-(bromophenylamino)-6-(4-pyridyl)pyrimidin-4-one (Compound 421)

Melting Point: 289-291℃.

NMR (DMSO-d_6, δ): 6.69 (br, 1H), 7.23 (m, 1H), 7.33 (t, J=8.1Hz, 1H), 7.65 (m, 1H), 7.96 (d, J=5.7Hz, 2H), 8.15 (s, 1H), 8.72 (d, J=5.7Hz, 2H).

m.p. : 289-291℃

Example 92: Preparation of 2-phenylamino-6-(4-pyridyl)pyrimidin-4-one (Compound 168)

Melting Point: 252-253℃.

NMR (DMSO-d_6, δ): 6.62 (s, 1H), 7.08 (t, J=7.8Hz, 1H), 7.39 (d, J=7.8Hz, 2H), 7.71 (d, J=7.8Hz, 2H), 7.95 (d, J=6.0Hz, 2H), 8.71 (d, J=6.0Hz, 2H), 9.00 (br, 1H), 10.95 (br, 1H).

Example 93: Preparation of 2-(3-methoxyphenylamino)-6-(4-pyridyl) pyrimidin-4-one (Compound 430)

Melting Point: 155℃.

NMR (DMSO-d_6, δ): 3.79 (s, 3H), 6.59-6.65 (m, 2H), 7.05-7.30 (m, 3H), 7.54 (s, 1H), 7.96 (d, J=5.7Hz, 2H), 8.71 (d, J=5.7Hz, 2H).

Example 94: Preparation of 2-(3,3-diphenylpropyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 396)

Melting Point: 297-299℃.

NMR (DMSO-d_6, δ): 2.49-2.55 (m, 4H), 4.05 (m, 1H), 6.86 (s, 1H), 7.10-7.20 (m, 2H), 7.26-7.37 (m, 8H), 7.97 (dd, J=1.5Hz, 4.5Hz, 2H), 8.69 (dd, J=1.5Hz, 4.5Hz, 2H).

Example 95: Preparation of 2-(2-naphthylmethyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 97)

Melting Point: >300°C.

NMR (DMSO-d_6, δ): 4.15 (s, 2H), 6.99 (s, 1H), 7.48-7.52 (m, 2H), 7.58 (d, J=10.2Hz, 1H), 7.87-7.92 (m, 4H), 7.96 (dd, J=1.5Hz, 4.5Hz, 2H), 8.68 (dd, J=1.5Hz, 4.5Hz, 2H), 12.96 (br, 1H).

Example 96: Preparation of 2-(3-phenylbenzyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 379)

Melting Point: 234-237°C.

NMR (DMSO-d_6, δ): 4.05 (s, 2H), 6.99 (s, 1H), 7.37-7.56 (m, 6H), 7.67 (dd, J=1.2Hz, 6.0Hz, 2H), 7.74 (s, 1H), 7.98 (dd, J=1.5Hz, 4.5Hz, 2H), 8.68 (dd, J=1.5Hz, 4.5Hz, 2H), 12.91 (br, 1H).

Example 97: Preparation of 2-(4-hydroxyphenyl)-6-(4-pyridyl)pyrimidin-4-one (Compound 416)

Melting Point: >300°C.

NMR (DMSO-d_6, δ): 6.87 (d, J=8.7Hz, 2H), 6.96 (s, 1H), 8.05-8.14 (m, 4H), 8.69 (dd, J=1.5Hz, 6.0Hz, 2H), 10.25 (br, 1H), 12.66 (br, 1H).

Test Example: Inhibitory activity of the medicament of the present invention against P-GS1 phosphorylation by bovine cerebral TPK1:

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β-mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μg/ml P-GS1, 41.7 μM [γ-^{32}P] ATP (68 kBq/ml), bovine

cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The results are shown in the table below. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the Aβ neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Table 2

Example	(Compound No.)	IC_{50} (μM)
1	(125)	2.3
2	(1)	3.0
5	(4)	2.1
6	(5)	1.3
7	(6)	2.4
12	(35)	1.8

14	(38)	4.0
15	(39)	2.2
16	(40)	4.8
19	(51)	8.7
22	(60)	6.2
24	(64)	5.3
27	(75)	3.3
28	(77)	1.3
29	(78)	1.4
31	(80)	2.9
33	(86)	5.5
35	(93)	8.9
36	(94)	0.50
37	(124)	3.8
38	(126)	1.8
42	(150)	7.6
43	(157)	5.7
44	(169)	3.7
68	(84)	1.3
69	(141)	2.5
71	(170)	1.1
79	(404)	2.8
80	(397)	1.1
82	(142)	4.3
83	(33)	2.8
84	(440)	1.1
85	(171)	0.96

86	(401)	10
87	(140)	2.6
88	(436)	1.4
89	(428)	2.3
90	(434)	6.3
91	(421)	1.6
92	(168)	1.6
93	(430)	1.8
96	(379)	0.77
97	(416)	1.7

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

(3) Parenteral preparations

The ingredients below were mixed by an ordinary method to prepare injections contained in a 1 ml ample.

Compound of Example 27	3 mg
Sodium chloride	4 mg
Distilled water for infection	1 ml

Industrial Applicability

The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as Alzheimer disease.